Research Article

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Evaluation of the Acute Kidney Injury Network criteria in hospitalized patients with cirrhosis and ascites

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Background & Aims: For several years hepatologists have defined acute renal failure in patients with cirrhosis as an increase in serum creatinine (sCr) ⩾50% to a final value of sCr >1.5 mg/dl (conventional criterion). Recently, the Acute Kidney Injury Network (AKIN) defined acute renal failure as acute kidney injury (AKI) on the basis of an absolute increase in sCr of 0.3 mg/dl or a percentage increase in sCr ⩾50% providing also a staging from 1 to 3. AKIN stage 1 was defined as an increase in sCr ⩾0.3 mg/dl or increase in sCr ⩾1.5-fold to 2-fold from baseline. AKI diagnosed with the two different criteria was evaluated for the prediction of in-hospital mortality.

Methods: Consecutive hospitalized patients with cirrhosis and ascites were included in the study and evaluated for the development of AKI.

Results: Conventional criterion was found to be more accurate than AKIN criteria in improving the prediction of in-hospital mortality in a model including age and Child-Turcotte-Pugh score. The addition of either progression of AKIN stage or a threshold value for sCr of 1.5 mg/dl further improves the value of AKIN criteria in this model. More in detail, patients with AKIN stage 1 and sCr <1.5 mg/dl had a lower mortality rate ($p = 0.03$), a lower progression rate ($p = 0.01$), and a higher improvement rate ($p = 0.025$) than patients with AKIN stage 1 and sCr ⩾1.5 mg/dl.

Conclusions: Conventional criterion is more accurate than AKIN criteria in the prediction of in-hospital mortality in patients with cirrhosis and ascites. The addition of either the progression of AKIN stage or the cut-off of sCr ⩾1.5 mg/dl to the AKIN criteria improves their prognostic accuracy.

Introduction

Renal failure is a common complication in patients with cirrhosis, occurring in approximately 20% of hospitalized patients [1]. A serum creatinine (sCr) ⩾1.5 mg/dl is the most commonly used criterion to diagnose renal failure in patients with cirrhosis [2]. However, this criterion is inadequate for the diagnosis of acute renal failure, which requires a dynamic evaluation of sCr value. A percentage increase in sCr ⩾50% to a final value ⩾1.5 mg/dl was the usual definition for the diagnosis of acute renal failure in patients with cirrhosis (conventional criterion) [3–6].

Nevertheless, in recent years other diagnostic criteria have been proposed for the diagnosis of acute renal failure. In particular, the Acute Kidney Injury Network (AKIN) recently developed and published a consensus definition of "Acute Kidney Injury" (AKI), a new term to define acute renal failure. AKI is defined as an abrupt (within 48 hours) reduction in renal function manifested by an absolute increase in sCr of 0.3 mg/dl, a percentage increase in SCr of 50% or more, or a reduction in urine output (documented oliguria of less than 0.5 ml/kg per h for more than six h) [7]. As urine collection and output documentation can be inconsistent, in clinical practice, creatinine kinetic becomes the fulcrum of the definition. This is particularly true in patients with cirrhosis and ascites, who can be oliguric as a result of avid renal sodium retention despite a normal glomerular filtration rate [8]. AKIN definition also permits a staging of AKI based on the entity of the variation of renal function over a slightly longer time frame, arbitrarily set at one week (Table 1). When compared with conventional criteria, the main innovative aspects introduced by

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Abbreviations: sCr, serum creatinine; AKIN, Acute Kidney Injury Network; AKI, Acute Kidney Injury; ADQI, Acute Dialysis Quality Initiative; ICA, International Club of Ascites; NSAIDs, non-steroidal anti-inflammatory drugs; SBP, spontaneous bacterial peritonitis; HRS, hepatorenal syndrome.

Table 1. Conventional criterion and Acute Kidney Injury Network (AKIN) criteria in the definition of Acute Kidney Injury (AKI) in patients with cirrhosis and ascites.

Conventional criterion	**Definition of AKI:**	A percentage increase in sCr of 50% or more to a final value of sCr >1.5 mg/dl
AKIN criteria	**Definition of AKI:**	An abrupt (within 48 h) increase in sCr of more than or equal to 0.3, percentage increase sCr of more than or equal to 50%
	Staging of AKI*:	Stage 1: increase in sCr ≥0.3 mg/dl or an increase in sCr ≥1.5-fold to 2-fold from baseline; Stage 2: increase in sCr >2-fold to 3-fold from baseline; Stage 3: increase of sCr >3-fold from baseline or sCr ≥4.0 mg/dl with an acute increase of at least 0.5 mg/dl

sCr, serum creatinine.
*Based on variation of sCr over a slightly longer time frame, arbitrarily set at one week.

AKIN criteria in patients with cirrhosis are the following: (a) an absolute increase in sCr is considered; (b) the threshold of sCr $\geqslant$1.5 mg/dl is not taken into account. In March 2010, the Acute Dialysis Quality Initiative (ADQI) and the International Club of Ascites (ICA) Working Group evaluated the application of AKIN criteria in cirrhosis, underlying the need to perform clinical studies to validate it [9]. During the EASL-ICA Joint Meeting in Berlin in March 2011, the ICA further stressed the need for new prospective studies on the same issue [10]. Nowadays, it has been shown that the development of AKI defined by AKIN criteria is a good predictor of in-hospital mortality in patients with cirrhosis and ascites and in critically ill patients with cirrhosis [11,12]. More recently, AKIN criteria have been shown to be associated with increased mortality among patients with cirrhosis who were hospitalized in regular wards in an AKIN stage-dependent fashion [13]. Nevertheless, the prognostic value of AKIN criteria has never been compared with the one of conventional criterion. Therefore, the aim of our study was to compare AKIN criteria and conventional criterion in the prediction of in-hospital mortality in a cohort of patients with cirrhosis and ascites.

Patients and methods

Patients population

The current study reports on the 233 consecutive patients with cirrhosis and ascites who were included in a prospective clinical study investigating prognosis in patients with cirrhosis and ascites in 2005 [14]. The study was approved by the local institutional ethical committee.

The diagnosis of cirrhosis was based on histological findings, when available, or on a combination of clinical, biochemical, ultrasonographic, and endoscopic findings. The presence of ascites was suspected by physical examination and confirmed by ultrasonography and/or diagnostic paracentesis.

Methods

sCr was measured in all the patients at admission and monitored daily during the hospitalization. The presence of hospital-acquired AKI was evaluated according to AKIN and conventional criteria, which are reported in Table 1. Patients with AKI diagnosed according to AKIN criteria were staged using the AKIN classification of acute renal failure. After the first fulfillment of AKIN criteria, the progressive changes in sCr values were monitored to document the evolution of AKI.

The diagnosis of bacterial infection was obtained according to clinical presentation by count of polymorphonuclear leukocytes, cultures of ascites, urine and blood, cultures of other organic fluids or secretions, chest X-ray or CT, US or CT of the abdomen, as previously reported in detail [14].

Defintion of AKI

For the definition of AKI with conventional criterion as well as with AKIN criteria, sCr at admission to the hospital was used as baseline sCr. According to AKIN criteria (Table 1), initial AKIN stage was defined by the AKIN stage at the time of the first fulfillment of the AKIN criteria. Progression of AKIN stage was defined by the progression to a higher AKIN stage during hospitalization. Peak AKIN stage was defined by the highest AKIN stage reached during hospitalization. Peak sCr was defined by the highest value of sCr reached during hospitalization. Resolution of AKI was defined by the lowering of sCr to the baseline value or less.

First-line treatments of AKI

In all patients with AKI and sCr <1.5 mg/dl, all nephrotoxic drugs as well as vasodilators and non-steroidal anti-inflammatory drugs (NSAIDs) were withdrawn. Diuretics were tapered or even withdrawn. Patients with bacterial infections received antibiotics according to the common guidelines. Bacterial infections were considered solved when all clinical signs disappeared, together with the normalization of laboratory, radiological, and microbiological findings.

Definitions of the different phenotypes of AKI and specific treatments

Prerenal AKI: AKI was considered as prerenal when patients had a history of fluid losses in the preceding days and when serum creatinine was normalized as a result of tapering or withdrawal of diuretics, and/or saline administration. AKI was considered prerenal also in patients with bacterial infections when sCr was normalized as a result of antibiotic treatment, and saline administration. Saline administration was provided only for patients with sCr >1.5 mg/dl according to the ICA criteria.

Parenchymal AKI: AKI was considered as parenchymal when there was either a history of recent or ongoing nephrotoxic drugs or proteinuria greater than 500 mg/24 h, abnormal urine sediment with more than 50 red cells per high-power field, or abnormal renal ultrasound findings in the absence of other causes of impairment of renal function. Renal replacement therapy (RRT) was considered for some patients with severe parenchymal AKI.

Hepatorenal syndrome (HRS): the old criteria of the International Club of Ascites (ICA) were used for the diagnosis of HRS in patients with AKI [15]. Nevertheless, for the purpose of the study, HRS was diagnosed in patients with AKI associated with bacterial infection when: (a) the bacterial infection was solved by the antibiotic treatment, (b) serum creatinine was not normalized by administration of saline, and (c) all the other criteria for HRS were fulfilled. These criteria were used instead of the most recent criteria of the ICA because the latter were published when the inclusion of patients in the current study was completed. Terlipressin plus albumin was used in patients with type 1 HRS and in those with severe type 2 HRS defined as sCr $\geqslant$2 mg/dl.

Statistical analysis

Statistical analysis was conducted with SAS 9.2 for Windows (SAS Institute Inc., Cary, NC, USA). Quantitative variables are reported as mean and standard deviation (SD) or median, minimum and maximum. Categorical variables are reported as count and percentage in each category.

Factors predicting AKIN stage progression or in-hospital mortality were identified in univariate analysis with Student's *t* test or Wilcoxon rank sum test for quantitative variables, Chi-square or Fischer's exact test for categorical ones. Since only one variable was statistically significant at the 5% level as predictor of AKIN stage progression, multivariate logistic regression model was not applied. Among all variables statistically significant at the 5% level as predictors of mortality, age and Child-Turcotte-Pugh (CTP) score were subsequently included in a multivariate logistic regression model while baseline sCr, peak sCr, and MELD score were excluded in order to avoid a multicollinearity with the conventional criterion as well as with AKIN criteria. Results of the multivariate analysis are presented as *p*-values, odds ratio, and 95% confidence interval. The comparison between conventional criteria and AKIN criteria in the prediction of mortality